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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/660,862	09/13/2000	William Pollack	ATOPH:52516	7947

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/660,862	POLLACK, WILLIAM	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 9, 2004 has been entered. Applicant's amendment and response are acknowledged. Claim 1 has been amended. Claims 2-4 and 10-13 have been cancelled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

3. Applicant's submission of a declaration under 1.132 is acknowledged. However, the declaration is insufficient to overcome the rejection of claims 1 and 5-9 under 35 U.S.C. 103(a) because the declaration does not address the current rejections of record in this application.

Rejection Maintained

4. The rejection of claims 1 and 5-9 under 35 U.S.C. 103(a) as unpatentable over Laursen et al in view of Flaa et al is maintained for the reasons set forth on pages 3-5, paragraph 4 of the Final Office Action.

The rejection was on the grounds that Laursen et al teach a method of producing immunoglobulins and other immunoglobulin products (see the Title). Laursen et al teach a method of producing IgG4 (see Example 2, columns 17-18 and column 20, lines 9-15). Laursen et al teach the use of DEAE Sepharose® and CM-Sepharose® exchange resins in the method of producing immunoglobulin and immunoglobulin products (column 7). Laursen et al teach a method of producing immunoglobulins by starting with normal human plasma or plasma from donor with high titers of specific antibodies (i.e. hyperimmune plasma) (column 4). Laursen et al teach that the method for producing IgG immunoglobulins and immunoglobulin products include: 1) purification of the Cohn fraction by preparing Cohn fraction from human plasma by adjusting the pH, ethanol concentration, adjusting temperature and protein concentration, 2) extraction of the immunoglobulin from the Cohn extraction by adding sodium phosphate, adjusting pH, filtering, centrifuging and re-filtering the suspension and 3) purification of by serial anion and cation exchange chromatography using DEAE Sepharose® and CM-Sepharose® resins. Laursen et al teach that the IgG is eluted with a gradient of NaCl when the CM-Sepharose column is used (column 15-16). Laursen et al teach the addition of saccharides to the IgG fraction to stabilize and adjust the osmolality of the IgG fraction (column 9, lines 17-26 and column 4, lines 20-23). Laursen et al teach an osmolality of 347-350 mOsm/kg (column 23) and a pH range of 4.0-6.0 for the IgG immunoglobulin fraction (column 5, lines 12-14). Laursen et al teach that the products obtained from the invention can be freeze-dried (column 12, lines 35-37). The recitation of "conductivity of between 3.5 to 6 millisiemens" would be an obvious experimental design choice. It is well known in the art to freeze and later thaw purified fractions at certain convenient points in the process of antibody purification. This is done to pool large amounts of purified antibody fractions before use or further processing or to store purified antibody fractions to be used at a later date. This is evidenced by Rhodes *(U.S. Patent No. 5,346, 687, published September 13, 1994),* which teaches that frozen purified antibody can be frozen in a vial and maintained for indefinite period before use (claim 5).

Laursen et al do not teach the use of lactose.

Flaa et al teach stabilizing solutions for proteins and peptides (see the Title). Flaa et al teach that bulking agents such as lactose can be added to protein compositions, if the protein compositions are going to lyophilized or frozen (column 5, lines 63-67 and column 6, lines 1-3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the lactose as taught by Flaa et al to the IgG4 composition of Laursen et al because Laursen et al teach that saccharides are added to stabilize the IgG fraction and to adjust the osmolality of the IgG fraction (column 9, lines 17-26 and column 4, lines 20-23). It would be expected barring evidence to the contrary that the method of producing IgG4 as taught by Laursen et al and Flaa et al combined would produce purified amounts of IgG4 because Laursen et al teach that purified amounts of IgG4 ranging from 0.6% to 1.5% are produced by the method (columns 17-18).

Applicant urges that in order to establish a *prima facie* case of obviousness the Office must demonstrate that the cited references provide a suggestion or motivation for their modification or combination, a reasonable expectation of success in the combination and that the reference teach or suggest all claim limitations. Applicant asserts that no *prima facie* case of obviousness has been established. Applicant urges that particular care must be taken to avoid use of hindsight in obviousness analysis. Applicant urges that Laursen et al discloses methods of purifying a total IgG preparation from plasma. Applicant urges that Laursen et al arrive at their disclosed product, a total IgG preparation which required subtype distribution close to that of blood. Applicant urges that Laursen et al do not disclose a purified IgG that consist essentially of IgG4. Applicant urges that there is no suggestion or motivation to modify or combine the cited references. Applicant urges that Laursen et al teach away from use of pH values greater than 6, the claimed 6.5 pH value. Applicant urges that the Office is incorrect in their assertion that Laursen et al teach a purified IgG4 preparation. Applicant urges that Laursen et al provide no clear and particular suggestion or motivation for its combination with Flaa et al to arrive at

the claimed invention. Applicant urges that Flaa et al only teach solutions for stabilizing purified proteins and do not teach any methods of purifying proteins, including immunoglobulins. Applicant urges that the modification of Laursen et al to arrive at purified IgG4 to be combined with Flaa et al would render the product unsuitable for the intended use. Applicant urges that even if the teachings of Laursen et al could be modified to arrive at a purified IgG4 preparation (Laursen specifically disclaim adjustment of plasma to pH values greater than 6.0), a purified IgG4 preparation would not be useful to treat diseases and conditions that benefit from replacement or supplementation of the total IgG component of blood. Applicant urges that the process of the prior art produces a different product. Applicant refers to the William Pollack Declaration that teaches that the product of the invention is mostly if not entirely IgG4. Applicant urges that the product is essentially free of all other subtypes.

Applicant's arguments filed August 9, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings with their assertion that "Flaa et al only teach solutions for stabilizing purified proteins and do not teach any methods of purifying proteins, including immunoglobulins". It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. Laursen et al teach a method of producing immunoglobulins including IgG4 that are stable up to 12 months. Laursen et al do not teach a method of manufacturing IgG4, wherein the monosaccharide is lactose. However, Flaa et

al teach that bulking agents such as lactose are added to protein compositions that are to be lyophilized or frozen. One would be motivated to add the lactose as taught by Flaa et al to the IgG preparations (including IgG4) of Laursen et al because Laursen et al teach that saccharides are added to stabilize the IgG fraction.

It appears that Applicant is arguing limitations that are not in the claims by asserting that "Laursen et al arrive at their disclosed product, a total IgG preparation which required subtype distribution close to that of blood" and the assertion that "that the modification of Laursen et al to arrive at purified IgG4 to be combined with Flaa et al would render the product unsuitable for the intended use." There is no limitation in the claims regarding quantity of IgG4 produced in the claimed method. It should be remembered that the claims are directed to a method of making an IgG4 preparation and not a method of using the product. Therefore, Applicant's comments regarding the intended use of the product are irrelevant. The Examiner disagrees with Applicant's assertion that the prior art teaches a different product because the prior art does not teach the same pH range used to produce the IgG4 of the claimed invention. The claimed invention is directed to a method of manufacturing IgG4, wherein the pH is adjusted to about 6.5. The prior art teaches that the pH of the IgG (including IgG4) range from 4.0 to 6.0, although lower pH ranges are mentioned in different embodiments of the invention. Therefore, the prior art does not teach way from the pH used to prepare the IgG4 of the claimed invention. It should be noted that "about" is entitled to latitude in characterizing feature which was not critical to

distinction over the prior art. *General Food Corp. v. Perk Food Co.* (DC. NIII) 157 USPQ 14. The Examiner is viewing a pH of 6 to mean a pH of about 6.5 since the lower limit of "about" has not been established.

In response to applicant's argument that there is no suggestion or motivation to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

To address Applicant's comments regarding the William Pollack Declaration, it appears that the declaration is referring to references (Zolton et al, Cheung et al, Sirna and Thomas) that are not apart of the pending rejection in this application. It should be remembered that the rejection in this application is under 35 U.S.C. 103(a), Laursen et al in view of Flaa et al. The declaration is

insufficient because it does not address the current rejection. Laursen et al and Flaa et al as combined teach a method of preparing purified IgG4. There is nothing on the record to show that the references as combined would not teach or suggest the claimed invention.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 5-9 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "about". It is unclear as to what the upper and lower limits are for the cited ranges of the pH and conductivity. It should be noted that "about" is entitled to latitude in characterizing feature which was not critical to distinction over the prior art. *General Food Corp. v. Perk Food Co.* (DC. NIII) 157 USPQ 14. Clarification is required.

6. Claims 1 and 5-9 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "obtained from". It is unclear as to what Applicant is referring? Clarification is required.

Status of Claims

7. No claims are allowed.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

VLF

Vanessa L. Ford
Biotechnology Patent Examiner
August 27, 2004

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